Visfatin, resistin, hsCRP and insulin resistance in relation to abdominal obesity in women with rheumatoid arthritis

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Abstract

Objective

The increasing incidence of overweight and obesity in modern societies, and the demonstration that adipose tissue produces numerous cytokines, increases interest of investigators in the associations between adipose tissue, adipokines, CRP and insulin resistance in rheumatoid arthritis (RA) and their possible role in the pathogenesis of this disease. The purpose of the study was to investigate serum levels of visfatin, resistin, hsCRP and insulin resistance in relation to abdominal obesity in patients with RA.

Methods

Serum levels of visfatin, resistin, hsCRP and glucose metabolism parameters were measured in 46 women with RA – 22 without abdominal obesity and 24 with abdominal obesity.

Results

Patients with RA and abdominal obesity showed significant lower visfatin levels (1.00±0.93 vs. 1.44±0.85 ng/ml; $p<0.05$) in comparison to those without abdominal obesity. We found significant correlations between levels of visfatin and resistin ($r=0.41$; $p<0.01$); and between resistin levels and hsCRP levels ($r=0.41$; $p<0.01$); resistin levels and leucocytes count ($r=0.36$; $p<0.05$); and resistin levels and ESR ($r=0.30$; $p<0.05$), in the whole investigated group. Visfatin as well as resistin did not correlate with anthropometric parameters or insulin resistance in whole patients with RA.

Conclusion

In patients with RA and abdominal obesity, in comparison to patients without abdominal obesity, significantly lower visfatin levels have been demonstrated. Resistin was associated with laboratory markers of inflammation. Positive correlation between levels of visfatin and resistin may suggest that visfatin plays a role in inflammation in RA.

Key words

Visfatin, resistin, obesity, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is the most common arthritic disorder characterised by immunologic dysfunction and systemic inflammation. In this disease, many proteins engaged in the inflammatory process are produced, like tumour necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-6, and C-reactive protein (CRP) (1). The increasing incidence of overweight and obesity in modern societies and the demonstration that adipose tissue produces numerous cytokines, increases interest of investigators in the associations between adipose tissue and adipokines, CRP, insulin resistance, in arthritis-like RA and their possible role in the pathogenesis of this disease (2-4). Contrary to expectations, some recent studies suggest benefits of higher body mass index (BMI) in patients with RA. An interesting study by Kaufmann *et al*. demonstrates that BMI equal or higher than 27 kg/m^2 in patients with RA are correlated with slower progression in the joint destruction process in comparison to patients with low BMI (5). Escalante *et al*. showed an inverse relationship between body mass and mortality in patients with RA (6). However, Bartfai *et al*. found no relationship between the prevalence of RA and BMI (2).

Visceral fat tissue, which is recognised as an endocrine and a paracrine organ, releases many bioactive molecules called adipokines, which influence metabolic processes such as insulin resistance, glucose and lipid metabolism, and immunologic and inflammatory reactions (4, 7, 8). Recently, the role of adipokines, among others, resistin, visfatin and low circulating adiponectin in inflammation and rheumatic disease has been intensively investigated (4, 9, 10, 11). Starting from the study of Holcomb *et al*. (12), who demonstrated that resistin structure is similar to protein identified in the site of inflammation, the role of resistin in inflammation was suggested. Stejskal *et al*. observed higher levels of resistin in subjects with acute inflammatory disease in comparison to healthy subjects or patients with type 2 diabetes mellitus (9). Recently, associations of visfatin and inflammation have also been discussed (13-15). Otero *et al*. showed higher circulating visfatin levels in patients with RA in comparison to healthy subjects (10). Moschen *et al*. showed that recombinant visfatin activates human leukocytes and induces cytokine production (14). Brentano *et al*. established Pre-B Cell Colony-Enhancing Factor/Visfatin as a proinflammatory and matrix-degrading mediator of joint inflammation in RA (13).

Because of existing controversies concerning associations between obesity and inflammatory process in RA, we investigated serum concentration of visfatin, resistin, hsCRP and insulin resistance in relation to abdominal obesity in patients with RA. Only postmenopausal women were included in the study due to the fact that gender and sex-hormones seem to influence serum resistin concentrations (16, 17).

Material and methods

The study group consisted of 46 women, aged 49 to 65 years with rheumatoid arthritis diagnosed according to the American College of Rheumatology criteria (18), who were treated in the Rheumatology Department between February and May 2007. Patients were divided into two groups according to waist circumference: group I – patients without abdominal obesity (n=22, waist circumference <80cm), group II – patients with abdominal obesity (n=24, waist circumference ≥80cm) (19). Patients with infection, cancer, uncontrolled metabolic disorders, kidney and liver insufficiency, coexisting with other systemic connective tissue diseases or treated with steroids (4 weeks before hospitalisation), biologicals and hormone replacement therapy were excluded from the study.

Disease activity score DAS28 was assessed in each patient, using the number of swollen and tender joints, patient's global visual analogue scale (VAS) and erythrocyte sedimentation rate (ESR) (20). Blood samples were taken from the antecubital vein from fasting patients between 8 and 9 am. Samples were centrifugated at 5000 rpm and 4ºC. Serum was separated and stored at -70ºC. ESR was measured using Medlab Products kit (Poland); leucocytes count was measured using Sysmex 1000 device

(Japan); glucose concentrations were determined using enzymatic method with Pointe Scientific Glucose-Oxy kit (USA). Serum concentrations of C-reactive protein (hsCRP) were determined with a high sensitive nephelometer method (Dade Behring, Germany) and insulin levels with a radioimmunological method (Bio-Source Europe S.A., Belgium). Serum concentrations of resistin and visfatin were analysed by an immuno-enzymatic ELISA method (R&D Systems, USA, assay sensitivity = 0.010 ng/ml, and ALPCO Diagnostics, USA, assay sensitivity = 30 pg/ml, respectively). Insulin sensitivity index HOMA-IR (Homeostasis Model Assessment Insulin Resistance) was calculated according to the Matthews formula (21).

The values are given as a mean, standard deviation, median and interquartile range. The Mann-Whitney U-test was used to evaluate significance of differences between groups. Correlations between variables were assessed using Spearman rank test. A p-value of <0.05 was taken to be statistically significant. All analyses were performed using Statistica 6.0 package.

The study protocol was approved by the Ethics Committee for Human Studies at K. Marcinkowski University of Medical Sciences in Poznan, and all participants gave their informed consent.

Results

Basic anthropometric and clinical characteristics in two groups of patients are presented in Table I. Body weight and BMI were significantly higher in patients with abdominal obesity in comparison to patients without abdominal obesity. There were no significant differences between groups with respect to age, disease duration, and disease activity score (DAS28). The results of the biochemical measurements are presented in Table II.

In patients with abdominal obesity, visfatin level was significantly lower than in patients without (p<0.05). Despite no significant difference in HOMA-IR between groups, the value of HOMA-IR (mean 3.05±1.93) in obese patients demonstrates insulin resistance in this group.

We found significant correlations between levels of visfatin and resistin (r=0.41; p<0.01) (Fig. 1); resistin levels and hsCRP levels (r=0.41; p<0.01) (Fig. 2); resistin levels and leucocytes count (r=0.36; p<0.05); and resistin levels and ESR (r=0.30; p<0.05), in the whole investigated group. There were significant correlations between BMI and waist circumference (r=0.60; p<0.01), glucose (r=0.37; p<0.05), insulin (r=0.32; p<0.05), HOMA-IR (r=0.43; p<0.01). There were no correlations of visfatin and resistin levels with anthropometric parameters, insulin resistance and DAS28.

Table I. Baseline characteristics in 46 rheumatoid arthritis patients.

Characteristic	Group I, without abdominal obesity (n=22)	Group II, with abdominal obesity (n=24)	p-value
Age (years)	55.0 (5.5); 53.0 (50-57)	56.0 (4.6); 56.0 (52-60)	0.1760
Age of menopause (years)	48 (4.9); 49.0 (46-50)	48 (4.2); 49.0 (45-52)	0.8832
Body weight (kg)	59.2 (7.4); 61.7 (53-64)	77.0 (10.2); 78.1 (69-86)	0.0000**
Height (cm)	160.1 (5.7); 160 (157-164)	160.6 (4.6); 161 (157-164)	0.7581
BMI (kg/m^2)	23.1 (2.7); 23.3 (21-25)	29.8 (3.4); 29.5 (27-33)	0.0000**
Waist circumference (cm)	75.8 (3.7); 76.5 (74-79)	96.1 (8.7); 98.5 (89-103)	0.0000**
Disease duration (years)	12.0 (8.8); 9.0 (5-15)	13.0 (8.0); 11.0 (6-17)	0.5024
Rheumatoid factor positive, n (%)	11 (50)	11 (46)	
DAS28	5.4 (1.0); 5.1 (5-6)	5.2 (0.9); 5.4 (5-6)	0.6053
ESR (mm/h)	28.0 (21.4);17.5 (11-39)	27.0 (15.0); 22.0 (16-37)	0.4885
Leucocytes (x10^9/l)	7.1 (2.5); 6.1 (5-8)	6.3 (1.6); 5.8 (5-7)	0.2962
DMARDs			
Methotrexate, n (%)	15 (68)	16 (67)	
Sulfasalazine, n (%)	5 (23)	4 (17)	
Chloroquine, n (%)	2 (9)	3 (13)	
Extraarticular manifestation:			
Any	13 (59)	14 (58)	
Subcutaneous nodules	4 (18)	4 (17)	
Secondary Sjögren's syndrome	2 (9)	1 (4)	
Pulmonary fibrosis	1 (5)		
Vasculitis cutaneous	1 (5)	2 (8)	
Vasculitis affecting other organs	1 (5)	1 (4)	
Limfadenopathia	2 (9)	1 (4)	
Episcleritis		2 (8)	

**p<0.01
Results are expressed as mean (SD); median (interquartile range).
BMI: body mass index; DAS28: disease activity score; ESR: erythrocyte sedimentation rate; DMARDs: disease-modifying anti-rheumatic drugs.

Table II. Results of biochemical measurements in patients with and without abdominal obesity.

Parameter	Group I, without abdominal obesity (n=22)	Group II, with abdominal obesity (n=24)	p-value
Visfatin (ng/ml)	1.44 (0.85); 1.38 (0.92–1.65)	1.00 (0.93); 0.64 (0.35–1.44)	0.0295*
Resistin (ng/ml)	14.59 (5.59); 13.01 (10.68–16.69)	11.86 (3.50); 12.28 (9.67–13.91)	0.2182
Insulin (μIU/ml)	10.98 (5.60); 9.45 (7.67–13.97)	13.82 (7.39); 12.40 (8.45–17.35)	0.1728
Glucose (mmol/l)	4.68 (1.63); 4.48 (3.89–4.73)	4.82 (1.05); 4.62 (4.19–5.02)	0.7332
HOMA-IR	2.29 (2.12); 1.75 (1.24–2.56)	3.05 (1.93); 2.57 (1.69–3.41)	0.0586
hsCRP (mg/l)	5.82 (5.66); 5.09 (0.89–9.33)	7.75 (10.28); 3.70 (1.71–6.62)	0.7332

*p<0.05
Results are expressed as mean (SD); median (interquartile range).
HOMA-IR : Homeostasis Model Assessment Insulin Resistance; hsCRP: C-reactive protein.

Discussion

We showed significantly lower visfatin levels in patients with RA and abdominal obesity in comparison to those without abdominal obesity. Interestingly, although it does not seem to have been published yet, significant correlation between levels of visfatin and resistin has been demonstrated, while there have been no associations of visfatin and resistin with anthropometric parameters and insulin resistance.

Although visceral fat tissue is recog-

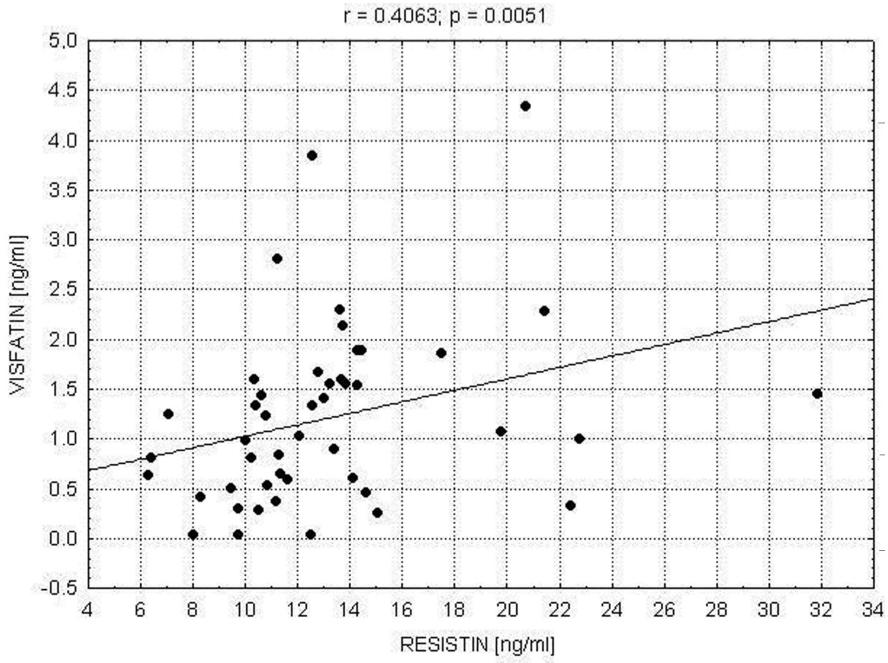

Fig. 1. Correlation between visfatin and resistin levels (r Spearman).

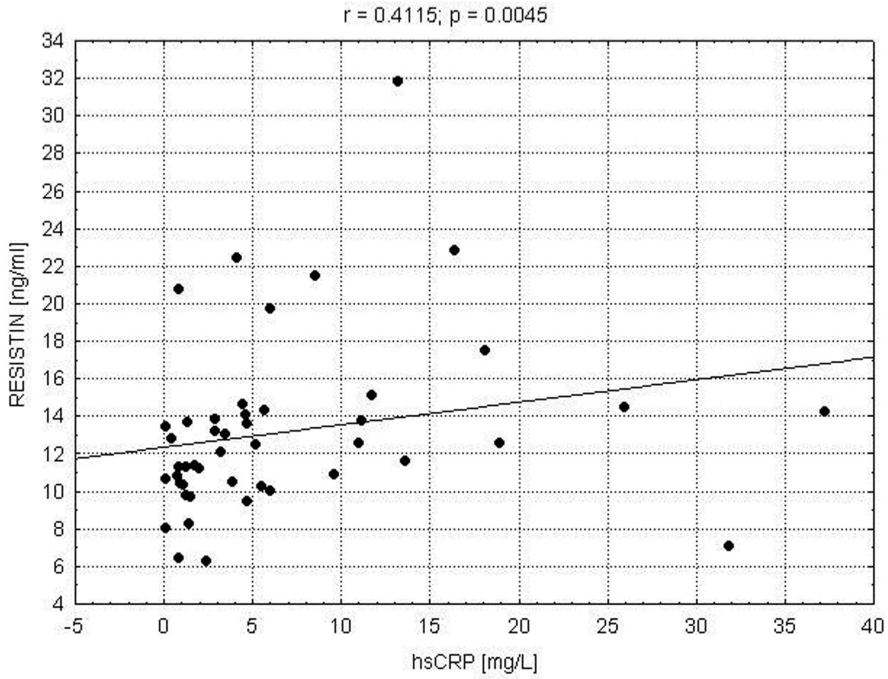

Fig. 2. Correlation between resistin and hsCRP levels (r Spearman).

nised as an endocrine and a paracrine organ releasing many bioactive molecules, several authors have reported that non-adipocyte fraction may be a significant component of the inflammatory state within the adipose tissue (22, 23). Circulating levels of visfatin are correlated with the amount of visceral fat in healthy subjects (24), even though visfatin is produced also by endotoxin-stimulated neutrophils. Visfatin synthesis is regulated by numerous factors, among others, glucocorticosteroids, TNF-α, IL-6 and growth hormone (3).

In the present study, interestingly, in contrast to the results obtained by Berndt *et al*. (25), while in accordance with Pagano *et al*. (26), we found significantly higher visfatin levels in patients without abdominal obesity in comparison to those with it. We also observed a significant correlation between visfatin and resistin levels in the whole investigated group. Since Brentano *et al*. (13) showed that PBEF/visfatin plays an important role in inflammatory and destructive processes touching the joints in patients with RA, our results can be compared with the outcomes of the research conducted by Kaufman *et al*. (5) who showed that low BMI might be a predictive factor for severe joint damage in RA. On the other hand, there were no significant differences between both investigated groups in inflammatory markers (hsCRP, leukocytes, ESR) and disease activity score (DAS28). It could not be excluded that lower visfatin levels in obese patients with RA in our study are the result of disturbed adipokines secretion and action in the course of obesity (27). It may also be possible that visfatin in peripheral tissue is influenced by negative feedback with other adipokines or other factors released by adipose tissue in RA, or via compensatory mechanism it facilitates the accumulation of intra-abdominal fat to prevent rheumatoid cachexia (10).

Visfatin is an insulin-mimetic adipokine (3). We did not observe in our study, as Chen *et al*. (28) did in female subjects, associations between visfatin levels and insulin resistance, or between visfatin levels and any anthropometric parameters (weight, body mass index, waist circumference). Contrary to Zahorska-Markiewicz *et al*. (29) we did not find associations between serum concentration of visfatin and insulin levels, but their study group consisted of obese women, 25 years younger than ours. Haider *et al*. (30) demonstrated in young healthy non-obese subjects, that visfatin concentrations are increased by hyperglycaemia, and this effect was prevented by co-infusion of insulin or somatostatin. Our study group was of about 30 years older, however Berndt *et al*. (25) reports that age is not an important factor related to visfatin levels.

We observed positive correlations between resistin levels and leucocyte count, and, like Migita *et al*. (31), between resistin and hsCRP levels, ESR in the whole group. Unlike Lee *et al*.

(32), we have not found associations between resistin levels and any anthropometric parameters, or insulin, glucose levels and HOMA-IR.

Concerning resistin levels in patients with RA, some studies reported no differences in comparison to healthy subjects (10), but some indicated higher levels of resistin comparing to healthy subjects (31), or patients with osteoarthritis (33), and its associations with inflammatory markers in the trial by Migita *et al*. – ESR, CRP, TNF-α (31), Forsblad *et al*. – CRP, TNF-α, IL-1Ra (17), Senolt *et al*. – CRP, DAS28, but not BMI (33), can be found. Forsblad *et al*. (17) has showed that resistin was associated with join destruction. According to a recent report in a group of RA patients who were subjected to anti-TNF-alpha blocker-infliximab therapy due to the severe disease refracting the disease modifying anti-rheumatic drugs (DMARDs), there is a significant association between the mean ESR and CRP taken during disease diagnosis, ESR and CRP and platelet count at the time of the study and baseline resistin levels. The study showed, as in our investigation, no significant correlation between serum resistin levels and BMI (34).

Thus, the positive correlations demonstrated in our study between resistin levels and some inflammatory markers (hsCRP, leucocytes and ESR) confirm the results of the above-cited investigators indicating that resistin may be considered a potential proinflammatory factor in RA, but its role does not seem be dependent on adiposity.

Kunnari *et al*. (16) in the population-based cohort study of 525 Finnish middle-aged subjects demonstrated, as in our study, associations of resistin levels and hsCRP, leucocytes, but not with insulin and glucose levels, and they suggest that inflammatory factors may more significantly determine resistin level than insulin and glucose levels.

The interesting study of Smith *et al*. (35) indicates a potential role of resistin in the pathophysiology of insulin- resistance syndrome in human subjects, while our findings do not demonstrate such associations. The mechanism of resistin contribution in insulin resistance is not clear. Nevertheless, severely diseased RA patients treated with infliximab infusions experienced a rapid improvement in insulin resistance and sensitivity (36) and a decrease in endothelial dysfunction biomarkers such as P-selectin (37).

While Azuma *et al*. (38) showed significantly higher serum resistin in obese subjects without RA than in lean volunteers, in our study we did not find a significant difference in resistin levels in patients with RA in relation to abdominal obesity. Lack of differences in resistin levels between our groups and no correlations between resistin levels and anthropometric features may suggest that other factors than adipose tissue determine resistin systemic concentrations in RA. As indicated by Toussirot *et al*. (4) proinfammatory cytokines (IL-1ß, IL-6 and TNF-α) cause increase in resistin expression in mononuclear blood cells. Gonzalez-Gay *et al*. (11) found low concentrations of adiponectin in patients with RA and suggested that high-grade inflammation originating from the joints may be a stronger determinant of impaired adiponectin production than adiposity in RA. They found the significant correlation between C-reactive protein levels and low circulating concentrations of adiponectin which is adipocyte-derived protein with anti-inflammatory, antiatherogenic and antidiabetic properties.

The consequences of systemic inflammation in RA are severe adverse effects which include accelerated atherosclerosis and increased cardiovascular mortality (39). Hurlimann *et al*. (40) and Gonzales *et al*. (41) revealed great efficacy of TNF-α blockers in improving function of endothelium in RA patients. Gonzalez-Gay *et al*. (34) showed a rapid reduction of resistin levels, and significant increase of ghrelin concentration (42) in patients with RA after anti-TNF-α therapy.

In conclusion, in patients with RA and abdominal obesity in comparison to patients without abdominal obesity significant lower visfatin levels are demonstrated. Resistin was associated with laboratory markers of inflammation. We have found positive correlation between levels of visfatin and resistin. Neither visfatin nor resistin correlated with anthropometric parameters or insulin resistance in patients with RA. Currently, the mechanism of fat tissue contribution in modulating inflammation in RA is not clear. Further studies are needed to explain the associations between fat tissue and adipokines in inflammatory diseases, concerning their proinflammatory and immunomodulating action as well as the occurrence of insulin resistance.

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